

REC'D 29 APR 2005

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 11207-33-228	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEPA/416)	
International application No. PCT/US03/39645	International filing date (day/month/year) 12 December 2003 (12.12.2003)	Priority date (day/month/year) 12 December 2002 (12.12.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68 and US Cl: 435/6		
Applicant REGULOME CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 08 July 2004 (08.07.2004)	Date of completion of this report 14 April 2005 (14.04.2005)
Name and mailing address of the IPBA/US Mail Stop PCT, Attn: IPBA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer <i>Gary Benzion</i> Gary Benzion Telephone No. 571.272.1600

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/39645

I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-193 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____
- ☒ the claims:
pages 194-208 as originally filed
pages NONE as amended (together with any statement) under Article 19
pages NONE filed with the demand
pages NONE filed with the letter of _____
- ☒ the drawings:
pages 1-18 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____
- ☒ the sequence listing part of the description:
pages 1-8 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(e)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of

- ☐ the entire international application,
☒ claims Nos. 4-52

because:

- ☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination (*specify*):

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 4-52

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-3, drawn to a method of profiling the genomic regulatory regions of a biological sample.

Group II, claim(s) 4-11, drawn to a positionally addressable polynucleotide array.

Group III, claim(s) 12-52, drawn to a method for profiling chromatin sensitivity.

The inventions listed as Groups I, II and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions are linked by the technical feature of the positional array. However, this feature is not special because it does not constitute an advance over the prior art. Fodor et al. (US 2001/0053519) teach and reduce to practice an array comprising all possible 10-mers (see example 2, beginning on page 12).

The special technical feature of invention group I, a method of profiling regulatory regions of a biological sample, is the use of a sample enriched for ACE's or ACE fragments and is not present in invention groups II and III. The special technical feature of invention groups III, a method for profiling chromatin sensitivity of a genomic region, is the use of a ratio measurement comprised of the signal of the test probe representing the modified cell type and the reference probe representing the unmodified cell type and is not present in invention groups I and II.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-3

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PCT/US03/39645**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-3</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-3</u>	NO
Industrial Applicability (IA)	Claims <u>1-3</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Lockhart et al. (UPN 6, 040,138, 21.02.2000).

Lockhart et al. teach (claim 1) step (1) contacting a sample of nucleic acid from a biological sample with a positionally addressable array of polynucleotides under conditions such that hybridization can occur, the sample of nucleic acids being enriched in ACEs (the p53 gene meets the limitations of ACE,) or fragments thereof at least 10 bp (see whole document, especially col. 2 lines 56-67, col. 3 lines 1-6, col. 5 line 7) and

(s) detecting loci on the array where hybridization occurs, wherein the ACEs are each a nucleotide sequence characterized as being hypersensitive to a DNA modifying agent relative to a nearby region when present in chromatin isolated from one or more cells, has a size in the range of 80-250 base pairs and is bound by one or more sequence-specific DNA binding factors (see col. 4 lines 53-54, col. 5 line 7) and wherein the array of polynucleotides comprises a plurality of polynucleotides, each affixed to a substrate, said plurality comprising different polynucleotides differing in nucleotide sequence and being situated at distinct loci of the array, said different polynucleotides being complementary and hybridizable to genomic DNA of said biological sample (see col. 3 lines 7-28). The p53 gene exhibits DNase I hypersensitivity, where DNase I is the DNA modifying agent. With regard to claim 2, Lockhart et al. teach the plurality of polynucleotides is at least 20, 000 different nucleotides (see col. 3 line 11). With regard to claim 3, Lockhart et al. teach the ACE is further characterized as having an intrinsic ability to confer hypersensitivity to the DNase I when excised from its native location and inserted into at least one different location in the genome of a cell of the same cell type, and having a greater hypersensitivity to the DNase I relative to the nearby region (see col. 5 line 7). Lockhart et al. teach p53, the p53 gene exhibits the aforementioned hypersensitivity to DNase I (a DNA modifying agent).

NEW CITATIONS

US 6,040,138 A (Lockhart et al.) 21 March 2000, see columns 3-5.

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NOTE ON INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

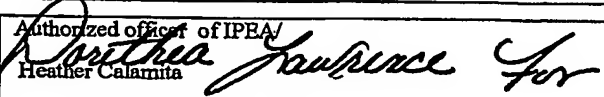
International application No. PCT/US03/39645	Applicant's or agent's file reference 11207-33-228	Date of informal communication (day/month/year) 13 April 2005 (13.04.2005)
Applicant REGULOME CORPORATION		

<u>Communication</u> <input checked="" type="checkbox"/> by telephone <input type="checkbox"/> personal	<table style="width: 100%;"> <tr> <td style="width: 40%;"><u>Participants</u></td> <td style="width: 20%;"><input type="checkbox"/> identity checked</td> <td style="width: 20%;"><input type="checkbox"/> authorization checked</td> <td style="width: 20%;"><input type="checkbox"/> personally known</td> </tr> <tr> <td><input checked="" type="checkbox"/> Applicant: REGULOME CORPORATION</td> <td colspan="3"></td> </tr> <tr> <td><input checked="" type="checkbox"/> Agent: Sebastian Martinek</td> <td colspan="3"></td> </tr> <tr> <td><input checked="" type="checkbox"/> Examiner(s): Heather Calamita</td> <td colspan="3"></td> </tr> </table>	<u>Participants</u>	<input type="checkbox"/> identity checked	<input type="checkbox"/> authorization checked	<input type="checkbox"/> personally known	<input checked="" type="checkbox"/> Applicant: REGULOME CORPORATION				<input checked="" type="checkbox"/> Agent: Sebastian Martinek				<input checked="" type="checkbox"/> Examiner(s): Heather Calamita			
<u>Participants</u>	<input type="checkbox"/> identity checked	<input type="checkbox"/> authorization checked	<input type="checkbox"/> personally known														
<input checked="" type="checkbox"/> Applicant: REGULOME CORPORATION																	
<input checked="" type="checkbox"/> Agent: Sebastian Martinek																	
<input checked="" type="checkbox"/> Examiner(s): Heather Calamita																	

Summary of communication:

I spoke with Sebastian Martinek on 13 April 2005 to request to do an IPER instead of a Written Opinion. Mr. Martinek indicated that it was ok to complete the IRER without first completing the Written Opinion.

- ☐ An extension of time limit is granted (Form PCT/IPEA/427).
- ☒ A copy of this note is being sent to the applicant with Form PCT/IPEA/429.

Applicant/Agent	Authorized officer of IPEA/  Heather Calamita Telephone No. (571) 272-1600
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